UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/812,393	03/05/97	SHERMAN L	313332000100

HM22/1109

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EXAMINER	
WILSON, M	
ART UNIT	**PAPER NUMBER**
1633	21

DATE MAILED: 11/09/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/812,393	Sherman et al.
Examiner	**Group Art Unit**
Wilson, Michael C.	1633

☒ Responsive to communication(s) filed on *Oct 8, 1999* .

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-21* is/are pending in the application.

Of the above, claim(s) *6-21* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-5* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *5 and 7*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Election/Restriction

1. Applicant's election of Group I, claim 1-5, in Paper No. 20 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 6-21 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b) as being drawn to a non-elected inventions. Election was made **without** traverse in Paper No. 20.

Claim 1-5 are under consideration in the instant application.

Claim Objections

2. Claim 5 is objected to because of the following informalities: The reference of primer in Figure 6 does not comply with C.F.R. 1.821 (d). The claim should specifically recite the SEQ ID Nos being claimed. Appropriate correction is required.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a preparing a nucleic acid molecule encoding a mouse T-cell receptor (TCR) which recognizes an antigen comprising administering the antigen to a transgenic mouse whose genome comprises a human HLA-A2 molecule wherein said mouse functionally expresses HLA-A2 on the surface of antigen presenting cells so as to allow presentation of the antigen with an HLA-A2 molecule such that recognition of the antigen and HLA-A2 molecule by cytotoxic T lymphocytes (CTL) occurs, isolating the CTL from the mouse, creating antigen-specific CTL populations and isolating the nucleic acid molecule encoding antigen-specific TCR using RT-PCR, does not reasonably provide enablement for preparing a nucleic acid molecule encoding a human HLA-restricted TCR specific for a TAA using any transgenic non-human vertebrate by cloning or amplifying a nucleic acid molecule as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claim 1 encompasses a method of preparing an isolated nucleic acid molecule comprising cloning or amplifying. Currently the only step claimed in the method of preparing an isolated nucleic acid molecule comprises "cloning or amplifying a nucleic acid molecule...." The omitted steps are: administering the antigen to a transgenic mouse, isolating the CTL from the mouse, creating antigen specific CTL populations which recognize the antigen. Then applicants step of cloning or amplifying appears to be next. Also omitted is a final step wherein the nucleic acid molecule encoding a TCR is isolated. The claim does not provide the appropriate steps required

required to isolate nucleic acids because cloning or amplifying does not result in obtaining a nucleic acid molecule. The steps of the method should flow according to the steps of the method taught in the specification and result in isolating a nucleic acid molecule.

Claim 1 is ~~directed toward~~ encompasses a transgenic non-human vertebrate which is modified so as to express at least one human HLA antigen. The state of the art of transgenics at the time of filing was and continues to be unpredictable. The individual gene of interest, promoter, enhancer, coding, or non-coding sequences present in the transgene construct, the site of integration, etc. are all important factors in controlling the expression of the transgene. Wall (1996, Theriogenology, Vol. 45, pages 57-68) discloses the unpredictability of transgene behavior due to factors such as position effect and unidentified control elements resulting in a lack of transgene expression or variable expression (paragraph bridging pages 61-62). Ebert et al. (1988, Mol. Endocrinology, Vol. 2, pages 277-283) teach a transgene encoding the human somatotropin gene operably linked to the mouse metallothionein promoter caused different phenotypes in transgenic pigs and mice (page 277, column 2, lines 17-27). Therefore, one of skill could also not predict whether a transgene expressed in a transgenic mouse will be expressed similarly or cause a similar phenotype in other animals. In fact, Overbeek (1994, "Factors affecting transgenic animal production," Transgenic animal technology, pages 96-98) teaches that within one litter of transgenic mice, considerable variation in the level of transgene expression occurs between founder animals and causes different phenotypes (page 96, last paragraph). The specification teaches using A.2.1/KbxCD8 or A2.1 transgenic mice (page 9, line 11) but does not provide any

guidance how to make any other transgenic non-human vertebrate. Given the differences in the expression of a transgene within a litter of transgenic mice and between transgenic mice and other animals, taken with the mere reference to the transgenic mice provided in the specification, it would have required undue experimentation to extend the transgenic mice referred to in the specification to other HLA molecules, other species or other phenotypes.

Claim 1 is directed toward a TCR which is human HLA-restricted. Applicants have used the phrase "HLA-restricted" in a manner which is not enabled because TCR are not HLA-restricted. It appears as though applicants are attempting to claim a TCR which only recognizes antigens in the presence of certain HLA molecules; however, TCR molecules by themselves may bind to other antigens to varying degrees and are not restricted to a particular HLA molecule because the TCR is not associated with a CTL. The accepted meaning of restriction is used to refer to antigens which are presented on an particular HLA molecule or CTL which only recognize an antigen presented on a particular HLA molecule. Therefore, CTL may be referred to as being HLA-restricted and antigens may be recognized in an HLA-restricted manner, but the TCR by itself is not HLA-restricted. For example, the melanoma associated antigen MART-1 is HLA-A2 restricted because it is presented on HLA-A2 molecules and is recognized by CTL only when presented on an HLA-A2 molecule (1997, Salazar-Onfray et al., Cancer Res., Vol. 57, pages 4348-4355). Therefore, MART-1 is an HLA-A2 restricted antigen and the CTL that recognize MART-1 are HLA-A2 restricted. The TCR isolated from the MART-1-specific CTL are referred to as being MART-1-specific TCR. Applicants have not defined the phrase "TCR

which is human HLA-restricted"; therefore, it would require one of skill undue experimentation to determine the metes and bounds of the characteristics of the TCR being claimed (see also 112/2nd paragraph rejection).

Claim 1 is directed toward a tumor associated antigen (TAA). Applicants have not enabled the breadth of the term because the art recognized meaning of the term may vary. For example, MART-1 is an antigen "associated" with melanoma, but it is also expressed in normal melanocytes (Fetsch et al., Feb. 1999, Cancer Cytopathology, Vol. 87, pages 37-42; see abstract). It is unclear whether applicants intend to claim an antigen only found in tumors or whether the antigen may be found in tumor as well as other tissues. The metes and bounds of the degree of association between the tumor and the antigen are not taught in the art or in the specification such the characteristics of the antigen could be determined (see 112/2nd paragraph rejection).

Claim 1 recites obtaining any non-human TCR from any non-human transgenic vertebrate. This encompasses obtaining a TCR of one species from transgenic vertebrate of another species. Applicants have only enabled obtaining mouse TCR from transgenic mice because applicants do not teach how to obtain a TCR of one species from transgenic vertebrate of another species.

Claim 1 recites a transgenic vertebrate which is modified so as to express at least one human HLA antigen. The entire HLA molecule must be expressed on the surface of an antigen-presenting cell to be of use in the instant invention. In addition, a vertebrate expressing only one human HLA molecule is not of use in the instant invention. The HLA molecules must be expressed to significant levels such that antigen recognition can occur and CTL that recognize the

antigen can be generated. Without adequate levels of HLA expression and production of CTL that recognize the administered antigen, the transgenic non-human vertebrate claimed is of no use.

Claim 5 recites a limitation "wherein said amplifying is effected by a polymerase chain reaction." Applicants have not enabled the term effected such that amplifying is effected by PCR such that a nucleic acid molecule encoding a TCR can be obtained. Amplifying is effected by temperature conditions, number of cycles and other parameters. Amplifying is not effected by PCR. Applicants should limit the claim to RT-PCR because the RNA and cDNA must be isolated before PCR takes place to isolate the nucleic acid encoding the TCR. Applicants have provided no other methods PCR amplification which can be used to isolate the nucleic acid molecule encoding a TCR.

Therefore, in view of the lack of guidance in the specification regarding how to make any transgenic non-human vertebrate whose genome comprises any HLA molecule and has any phenotype, the definition of the term "associated" and "restricted", the lack of correlation between the HLA-A2 transgenic mice and other transgenic non-human vertebrates, the state of the art, the examples provided and the breadth of the claims, the ordinary artisan at the time of the instant invention would not have known how to make and/or use the claimed invention with a reasonable expectation of success.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claim does not recite step of the method which result in isolating a nucleic acid molecule or in such a way that logically flows from the teachings of the specification. Immunizing a transgenic non-human vertebrate appears to be the first step in applicants method; however, immunization is not a step in the method claimed. Instead applicants have used the step of immunizing a vertebrate in describing the CTL. The creation of CTL which recognize an antigen appears to be another step in applicants method; however, the phrase is not included in the claims. Instead applicants included in the claims as a step in the method of preparing a nucleic acid but is included in the claim in a phrase describing CTL after the TCR has been cloned. The claim is confusing because the immunization occurs, then the CTL are made prior to cloning which is not the order recited in the claims and because the claim does not reflect the steps taught in the specification. Applicants should clearly recite all the steps involved in preparing the nucleic acid in a manner which logically flows from the teachings in the specification.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. Currently the only step claimed in the method of preparing an isolated nucleic acid molecule comprises "cloning or amplifying a nucleic acid molecule...." The omitted steps are: administering the antigen to a transgenic mouse, isolating the CTL from the mouse, creating

antigen specific CTL populations which recognize the antigen. Then applicants step of cloning or amplifying appears to be next. Also omitted is a final step wherein the nucleic acid molecule encoding a TCR is isolated.

While applicant may be his or her own lexicographer, a term in a claim may not be given a meaning repugnant to the usual meaning of that term, *In re Hill*, 161 F.2d 367, 73 USPQ 482 (CCPA 1947). The term "TCR is human HLA-restricted" in claim 1 is used by the claim to mean "a TCR which only recognizes certain HLA molecules," while the accepted meaning is used to refer to antigens which are presented on an particular HLA molecule or CTL which only recognize an antigen presented on a particular HLA molecule.

The term "associated" in claim 1 is a relative term which renders the claim indefinite. The term "associated" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is unclear how the antigen is associated to tumor cells.

The term "restricted" in claim 1 is a relative term which renders the claim indefinite. The term "restricted" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is unclear how restricted the T-cell receptor is to HLA-expressing cells, tumor antigens or other molecule.

The phrase "a non-human TCR which TCR is human HLA-restricted" is indefinite because it is unclear how a non-human TCR is restricted to humans or to HLA (see 112/1st rejection).

Claim 1 is indefinite because it is unclear from the phrase "encoding at least one of the variable regions of the a and b chains" whether applicants intend to claim at least one variable region which can be either α or β chain or whether applicants intend to claim at least one α chain and one β chain.

Claim 1 is indefinite because the phrase "said encoding nucleotide sequence" (line 5) lacks antecedent basis in the claim.

Claim 4 is indefinite because the term "effected" is unclear as used in the claim. Amplifying is effected by temperature conditions, number of cycles and other parameters. Amplifying is not effected by PCR. It is unclear what the metes and bound of the claim are.

Claim 5 is indefinite because the term "essentially" is not defined in the specification such that the essential elements of the primers could be determined. The metes and bounds of the claim cannot be determined.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Man et al. (1994, J. Immunol., Vol. 153, pages 4458-4467) in view of Cole et al. (April 1995, FASEB Journal, Vol, 9 page A801, abstract 4638).

Man et al. teach administering the influenza A antigen, $M1_{(58-66)}$, to transgenic mice expressing HLA-A2.1 and obtaining cytotoxic T cells which recognize the M1 (page 4459, column 1, "influenza-specific CTL from HLA-A2.1 transgenic mice"). The nucleic acid molecule encoding the α and β chain of the TCR were isolated by PCR (page 4459, column 2, "PCR amplification and sequencing of TCR α- and β-chain cDNA). The primers used by Man et al. were mouse α and β TCR-specific primers Vβ8, Vβ5 and Vβ6. The primers taught by Man et al. are essentially the which are essentially the primers Vβ8.1, Vβ8.2, Vβ8.3, Vβ5.1 and Vβ6 primers in Fig. 6. because the primers share homology and both serve the essential function of identifying the Vβ8, Vβ5 and Vβ6 chains of the TCR. Man et al. does not teach using the transgenic mouse to identify tumor associated antigens.

However, at the time of filing a number of tumor associated antigens which were HLA-A2 restricted were known in the art at the time of filing and could have replaced the $M1_{(58-66)}$. For example, Cole et al. teach the melanoma associated antigen MART-1 which is recognized by CTL in an HLA-A2 restricted manner. Cole et al. teach generating MART-1-specific, HLA-A2 restricted CTL and isolating the TCR gene from the CTL (see entire abstract).

Therefore, it would have been obvious to use the method of isolating TCR genes from transgenic mice taught by Man et al. to obtain TCR genes specific for the MART-1 antigen.

Motivation to isolate TCR genes is from tumor associated antigen is provided by Cole et al. by teaching obtaining CTL which are specific for MART-1 and isolating the TCR receptors which are specific for MART-1 antigen (line 6). One of ordinary skill would have been motivated to replace the M1 antigen with the MART-1 antigen to obtain MART-1 specific TCR *in vivo*. One of ordinary skill would have had a reasonable expectation of success in delivering the MART-1 antigen because the antigen was easily made at the time of filing. One of ordinary skill would have had a reasonable expectation of isolating MART-1 specific TCR because MART-1 was known to be highly immunogenic.

Thus, Applicants' claimed invention as a whole is *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson whose telephone number is (703) 305-0120. The examiner can normally be reached on Monday through Friday from 8:30 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jasemine Chambers, can be reached on (703) 308-2035. The fax phone number for this Group is (703) 308-8724.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 305-0196.

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Karen M. Hauda

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Primary Examiner